Comparison Between End-to-end Anastomosis and Buccal Mucosa Graft in Short Segment Bulbar Urethral Stricture: a Meta-analysis Study

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ABSTRAK

Tujuan: *membandingkan keluaran jangka panjang antara teknik operasi end-to-end urethroplasty dan buccal mucosal graft.* ***Metode:*** *kami melakukan penelitian meta-analisis dari studi kohort. Pencarian literatur dilakukan pada database MEDLINE, Science Direct, dan EMBASE menyertakan penelitian-penelitian sejak tahun 1980 hingga 2014. Kriteria inklusi yang digunakan pada penelitian ini adalah pasien dengan striktur uretra bulbar ukuran pendek (≤3 cm) yang menjalani terapi end-to-end anastomosis (EE) dan buccal mucosa graft (BMG), serta mengalami keluhan berkemih dan disfungsi seksual ≥12 bulan. Pooled risk ratio (RR) dan interval kepercayaan 95% (95% CI) dihitung menggunakan metode Mantzel-Haenzel, sementara heterogenitas ditentukan melalui nilai* I^2*. Analisis data dilakukan menggunakan program lunak Stata versi 10.0 (Stata Corp).* ***Hasil:*** *kami menganalisis 10 studi dalam meta-analisis kali ini. Disfungsi seksual pasca EE ditemukan pada 24,6% (45/183) pasien, sementara pasca BMG ditemukan pada 9,1% (11/122) pasien (overall RR 2,54; 95% CI: 1,44–4,47; p=0,001). Keluhan berkemih pasca EE ditemukan pada 14% (8/57) pasien, sementara pasca BMG ditemukan pada* 1^2*,5% (7/56) pasien (overall RR 0,77; 95% CI: 0,3–2,0; p=0,591). Lebih jauh lagi, rekurensi striktur pasca EE ditemukan pada 8,4% (8/107) pasien, sementara pasca BMG ditemukan pada 30% (14/46) pasien (overall RR 0,38; 95% CI: 0,17-0,84; p=0,016). Efektivitas EE dan BMG terbukti sama dan keduanya menunjukkan komplikasi yang sedikit. BMG didapatkan lebih superior dibandingkan dengan EE dalam hal komplikasi disfungsi seksual yang minimal. Sementara itu, EE didapatkan lebih superior dibandingkan BMG dalam hal rekurensi striktur setelah operasi striktur uretra bulbar pendek.* ***Kesimpulan:*** *BMG bisa dipertimbangkan sebagai tataksana lini pertama dibandingkan EE dalam menangani kasus-kasus striktur uretra ukuran pendek.*

Kata kunci: *disfungsi seksual, keluhan berkemih, end-to-end anastomosis, buccal mucosa graft, striktur uretra anterior.*

ABSTRACT

Aim: *to compare long term follow-up between end-to-end urethroplasty and bucal mucosal graft for the management of patients with short bulbar urethral stricture.* ***Methods:*** *we conducted a meta-analysis of cohort studies. Literature research was performed on the MEDLINE, Science Direct, and EMBASE database including studies from 1980 through 2014. The inclusion criteria were patients with short bulbar urethral strictrure (sized ≤3 cm) undergoing end-to-end anastomosis (EE) and buccal mucosa graft (BMG) with the complication of voiding symptoms and sexual dysfunction ≥12 months. Pooled risk ratio (RRs) and 95% confidence interval (CIs) were calculated using Mantzel-Haenzel method, while the heterogeneity were determined through* I^2 *value.*

Data analysis were done using Stata software version 10.0 (StataCorp). ***Results:*** *We analyze 10 studies in this meta-analysis. Sexual dysfunction following EE and BMG were found in 24.6% (45/183) patients and 9.1% (11/122) patients, respectively (overall RR 2.54; 95% CI: 1,44-4,47; p=0.001). Voiding symptoms following EE and BMG were found in 14% (8/57) patients and 12.5% (7/56) patients, respectively (overall RR 0.77; 95% CI: 0.3–2.0; p=0.591). Furthermore, stricture recurrent following EE and BMG were 8.4% (8/107) and 30% (14/46), respectively (overall RR 0.38; 95% CI: 0.17–0.84; p=0.016). The effectiveness of EE and BMG were found to be equal as both demonstrated few complications. BMG were found to be superior than EE terms of minimal sexual dysfunction complication. On the contrary, EE were found to be superior than BMG in terms of stricture recurence following short bulbar urethral stricture surgery.* ***Conclusion:*** *BMG can be considered as the primary treatment rather than EE for managing short urethral stricture cases.*

Keywords: *sexual dysfunction, voiding symptoms, end-to-end anastomosis, buccal mucosa graft, anterior urethral stricture.*

INTRODUCTION

Anterior urethral stricture is a pathological condition in which a fibrous tissue involves the corpus spongiousum. The most common etiology of anterior urethral stricture is trauma, especially straddle injury. Several factors were taken into account in the management of anterior urethral stricture, such as etiology of stricture, site, length and density of the fibrous tissue.[1]

In previous years, the most common treatment for urethral stricture were urethral dilatation and direct vision internal urethrotomy (DIVU) or Sache. These treatments were preferred because they are simple with low morbidity.[2] However, in a previous study, the efficacy of these treatment was relatively low. Pansadoro et al.[3] evaluated 224 patients with anterior urethral stricture in 5 years and they found high recurrence rate after first, second and third procedure (58%, 82%, and 100% patients, respectively). Heyns et al.[4] found that the recurrence rate after first, second, and third procedure were 39%, 100% and 100%, respectively.

End-to-end urethroplasty (EE) was first introduced in 1919 by dr. Hamilton Russel. This procedure showed better result than DIVU.[5] End-to-end urethroplasty is ideally suited for bulbar stricture with ≤3 cm long.[6] High success rate were found in end-to-end uretroplasty. William et al.[7] followed up 168 patients and found the EE success rate approximately 95% in patients with 1.7 cm of average stricture length within 70 month of average follow up.[2] Other studies found that the success rate of EE procedure was 98.8% in 260 bulbar stricture patients with stricture mean length of 1.9 cm within 50 months average of follow-up.[5]

El-Kasaby in 1993 introduced the first buccal mucosal graft (BMG) from the lower lip for treatment of penile and bulbar urethral stricture.[7] Ventral, dorsal,[8,9] and lateral approach was used in BMG. The dorsal approach was also known as Barbagli procedure.[7,10] Usually, BMG was used for bulbar stricture more than >3cm long,[9] but several studies showed that BMG had superior success rate than end-to-end urethroplasy in the management of short bulbar stricture. In addition, Santucci et al.[11] found that BMG had fewer numbers of complications than EE urethroplasty in patient with average stricture length 1.4 cm.

Today, management of short anterior urethral stricture is controversial and there are only few researches that compared long term follow-up between EE and BMG in short bulbar urethral stricture. Therefore, we conduct a meta-analysis study to compare long term follow-up between EE and BMG in short bulbar urethral stricture.

METHODS

To obtain literature, an exhaustive electronic search was performed using MEDLINE, Science Direct, and EMBASE database, from 1980 to June 2014 using keywords "Long Term Follow-up", "Anterior Urethral Stricture", "End-to-End Urethroplasty", "Anastomotic Urethroplasty", and "Buccal Mucosa Graft".We restricted the search to articles published in English. Finally,

we checked references from relevant publications and review articles.

Eligibility Criteria

Prospective and retrospective cohort studies about short segment bulbar urethral stricture were included if the studies included treatment in man adult (>18 years old), patient with short bulbar urethral stricture (≤3 cm) who is treated by end-to-end urethroplasty (EE) and buccal mucosa graft (BMG), has sexual dysfunction (erectile dysfunction, chordate, cold glans, decrease glans sensitivity, penile length and impotence), voiding symptoms (post voiding dribbling, post void leak and stream spraying), has stricture recurrence (undergoes additional treatment after urethroplasty such as urethral dilatation, Sache, graft urethroplasty, etc that diagnosed by voiding cystourethrography, urethrography and/or uroflowmetry), and followed-up for more than 12 months. Patients with strictures located in prostatic, membranous and pendulous strictures, caused by pelvic fracture, non-English articles, case reports, or case series were excluded.

Quality of study was assessed by reviewing papers titles and abstracts. In the first screening, the first and second authors assessed all of the abstracts retrieved from the search and then obtained the full manuscripts of the citations that met the inclusion criteria. These authors evaluated the studies' eligibility and quality, and they subsequently extracted the data. Any discrepancies were solved by agreement and, if needed, they reached a consensus with the third author. Selection criterias of included studies from database are presented in **Table 1**.

Statistical Analysis

A fixed-effects model with Mantzel-Haenzel method was used to calculate the pooled Risk Ratio (RRs) and 95% Confidence Interval (CIs) by comparing between EE and BMG in sexual dysfunction and voiding symptoms in short bulbar urethral stricture. We assessed the heterogeneity by calculating the I^2 statistic and divided into: low (25%-50%), moderate (50%-75%) and high (>75%). All analyses were performed with Stata statistical software, version 10.0 (StataCorp).

Table 1. Selection criteria of includes studies (PICOS)

	Included	Excluded
Population	Patients with short bulbar urethral stricture ≤3 cm	stricture in prostatic, membranous, pendulous stricture, caused by pelvic fracture
Intervention	Urethroplasty	Internal uretrotomy
Comparison	End-to-end anastomosis and buccal mucosal graft (BMG)	
Outcome	Sexual dysfunction and voiding symtomps	
Study	Any type	

RESULTS

Methodological Quality

Assesment of study quality was conducted according to the Newcastle Ottowa-Scale (NOS). The scale contains 9 items, and each item accounts for 1 point. Among the included study, quality scores ranged from 3 to 8 points and summarized in **Table 2**. The process of identifying eligible studies is summarized in **Figure 1**. We selected 314 publication from database in which 273 out of those 314 publications were excluded based on title. Fourty one potentially eligible publications were assessed in detail, and 10 publications met the eligibility criteria, one of them is obtained from the author.

Sexual Dysfunction

There were 305 patients from 6 journals, comprised of 183 patients (EE) and 122 patients (BMG). We found 45 patients with sexual dysfunction from 183 patients EE (average follow-up 26.6 months and complication rate 24.6%) and 17 patients from 122 patients BMG (average followup 26.6 months and complication rate 9.1%). (**Table 2**)

Overall risk ratio from 6 journals about sexual dysfunction is 2.54 (95% CI, 1.44-4.47) and 95% Cl does not cross the line of no effect (line RR=1). It shows that BMG is better than EE based on sexual dysfunction in short bulbar urethral stricture (≤3 cm) management, statistically significant p=0.001 and I^2=0%. (**Figure 2**)

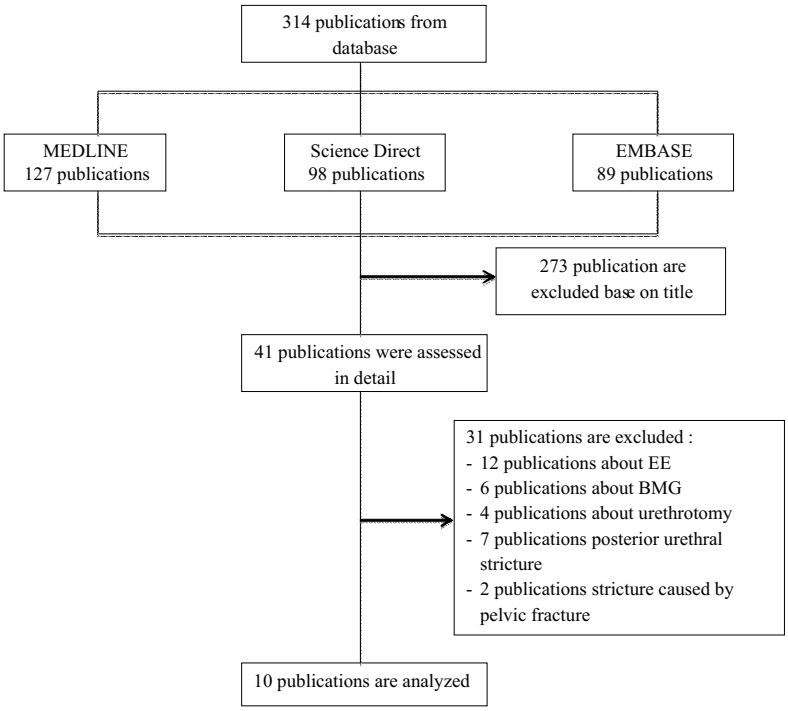

Figure 1. Literature search

Voiding Symptoms

Patient complaint. There were 113 patients from 3 literatures, comprises of 57 patients (EE) and 56 patients (BMG). We found 8 patients with voiding symptoms in patient complaint category from 57 EE patients (average follow-up 26.3 months and complication rate 14%) and 7 patients from 56 BMG patients (average follow-up 26.3 months and complication rate 12,5%). (**Table 3**)

Stricture recurrence. There were 153 patients from 3 literatures, comprised of 107 patients (EE) and 46 patients (BMG). We found 9 patients with voiding symptoms in stricture recurrence category from 57 EE patients (average follow-up 34months and complication rate 8,4%) and 14 patients from 46 BMG patients (average followup 34 months and complication rate 30%). (**Table 3**)

Overall risk ratio from 3 literatures about voiding symptoms in patient complaint category is 0,77 (95% CI 0.30 – 2.00) and 95% Cl cross the line of no effect (line RR=1). It is not statistically significant between EE and BMG, p=0.591 and I^2=28.5%. (**Figure 3**)

Overall risk ratio from 3 journals related to voiding symptoms in stricture recurence category is 0.38 (95% CI 0.17 – 0.84) and 95% Cl does not cross the line of no effect (line RR=1). It shows EE is better than BMG based on voiding symptoms in stricture recurence category in short bulbar urethral stricture (≤3 cm) management statistically significant p=0.016 and I^2=59.1%. (**Figure 3**)

DISCUSSION

Basically the surgical technique used in the repair of the bulbar urethral stricture might be selected according to stricture length and location. Generally, management for short urethral stricture use end-to-end urethroplasty and for long urethral stricture use graft.[21]

In this meta-analysis, we consider any risk factors for re-stricture, voiding problems, or sexual function after urethroplasty management in urethral stricture besides the operative technique and stricture length, such as operative time, younger patient age, multiple comorbidities (diabetes mellitus, hypertension, poor hemostasis), high litotomy position and history of urethroplasty.[18] Only few publications that explained about patients' history causing urethral stricture such as catheter-induced,

Table 2. Literature characteristics based on sexual dysfunction

No	Literature	Research method	Year	Mean of followup (month)	Samples	Follow-up method	Mean of stricture length (cm)	EE		BMG		Quality score
								Patient	Compli-cation	Patient	Compli-cation	
1	Coursey et al[13]	Prospective cohort study	2001	36	200 consecutive unselected men with a mean age plus or minus standard deviation of 43.8 ± 2.38 years who underwent anterior urethral reconstruction performed by 1 of 5 subspecialist recons-tructtive urological surgeons in 5 study centers. Patients were divided into groups based on the type of surgery performed, which use: 1. anastomotic urethroplasty, or, 2. buccal mucosal graft urethroplasty	Questionnaire (The questionnaire was formulated to assess perceived changes in satisfaction with erection, erect penile length and angle, and changes in these parameters with time. Alterations in the frequency of intercourse and changes in patient erection noted by their partners were also recorded. Each question achieved a relevancy score of greater than 90% with the Content Validity Index scale)	1.8	56	15	26	5	8
2	Al-Qudah et al[12]	Retrospective cohort study	2006	29	A retrospective of 60 consecutive patients who underwent 62 urethroplasty operations, including 24 anterior anastomotic and 19 buccal mucosa grafts	All spontaneous complaints were meticulously recorded. Further “open format” questioning allowed maximum patient reporting of all complications, no matter how minor.	2.8	24	5	19	0	7
3	Kessler et al[14]	Prospective cohort study	2007	18	A consecutive series of 267 patients underwent surgery for urethral strictures was studied prospectively. The surgical techniques used were based on concepts devised and popularized by Turner-Warwick for anastomotic urethroplasty, and Barbagli et al for buccal mucosa graft repair	Followed thereafter by assessment of erectile disfunction symptoms	2.9	20	10	23	4	8
4	Mac-Donald et al[15]	Retrospective cohort study	2005	24	We reviewed the records of 54 consecutive patients who underwent urethoplasty performed by a single surgeon. The procedures include 34 anastomotic and 20 buccal mucosal grafts	Patient complaints of erectile dysfunction and chordee	2.5	23	1	14	6	6

Table 2. Literature characteristic base on sexual dysfunction

No	Literature	Research method	Year	Mean of followup (month)	Samples	Follow-up method	Mean of stricture length (cm)	EE		BMG		Quality score
								Patient	Compli-cation	Patient	Compli-cation	
5	Dogra et al[16]	Prospective cohort study	2011	17	89 patients underwent single-stage anterior urethroplasty by senior consultant urologists in India.	All patients completed a preoperative IIEF-5 questionnaire to ascertain baseline sexual function and a repeat IIEF was given to all patients on consequent postoperative	2.95	32	9	21	2	6
6	Santucci et al[11]	Retrospective cohort study	2006	36	Retrospective chart review of 47 urethroplasty patients (19 buccal and 28 anterior anastomotic)	Early and late complication of erectile dysfunction and chordee	1.4	28	5	19	0	7
						Total		183	45	122	17	

Table 3. Literature characteristic base on voiding symptoms

No	Literature	Research method	Year	Mean of followup (month)	Samples	Follow-up method	Mean of stricture length (cm)	EE		BMG		Quality score
								Patient	Compli-cation	Patient	Compli-cation	
PATIENT COMPLAINT												
1	Al-Qudah et al[12]	Retrospective cohort study	2006	29	A retrospective chart review of 60 consecutive patient who underwent 62 urethroplasty operations, including 24 anterior anastomotic and 19 buccal mucosa graft	All spontaneous complaints were meticulously recorded. Further “open format” questioning allowed maximum patient reporting of all complications, no matter how minor.	2.8	24	5	19	2	7
2	Kessler et al[14]	Prospective cohort study	2007	18	A consecutive series of 267 patients undergoing surgery for urethral strictures was studied prospectively. The surgical techniques used were based on concepts devised and popularized by Turner-Warwick for anastomotic urethroplasty, and Barbagli et al for buccal mucosa graft repair.	Patients were followed thereafter by assessment of voiding symptoms (stream deteriorated) and urinary flow rate.	2.9	20	3	23	2	8

Table 3. Literature characteristic base on voiding symptoms

No	Literature	Research method	Year	Mean of followup (month)	Samples	Follow-up method	Mean of stricture length (cm)	EE		BMG		Quality score
								Patient	Compli-cation	Patient	Compli-cation	
3	Joseph et al[17]	Prospective cohort study	2002	32	During 32 months period, 69 men with previous management of urethral stricture disease were treated in London. The stricture was treated with excision of the stricture site with end-to-end anastomosis, while buccal mocosa graft as described by barbagli was performed in 14.	Follow-up of voiding symptoms (fistula and post void dribbling) from patient complaint	2.8	13	0	14	3	6
						Total		57	8	56	7	
STRICTURE RECURRENCE												
1	Lewis et al[18]	Retrospective cohort study	2002	24	Reviewed the records of 121 consecutive urethroplasties that were performed by a single surgeon. Complete data were analyzed on the 78 cases in which 1-stage anterior urethral reconstruction was performed via excision with primary anastomosis, a buccal mucosa graft	All patients had more than 1 year of followup. Uroflowmetry and urethrography were performed after 3 months and 1 year.	3	31	3	22	12	8
2	Park et al[19]	Retrospective cohort study	2004	25	We identified 78 male patients, 13 to 73 years old who were eligible in the urological trauma. Surgical managements of urethral stricture were end-to-end anastomosis and buccal mucosa graft	Follow-up with combination of retrograde urethrogram and voiding cystourethrogram	2.7	52	2	5	0	6
3	Barbagliet al[20]	Retrospective cohort study	1997	53	98 male patients underwent surgical treatment for urethral stricture by the same group of 3 urologic surgeon. The surgical procedures employed were excision and end-to-end anastomosis and buccal mucosa graft urethroplasty	All patients were followed-up with voiding cystourethrography, urethrography and uroflowmetry.	2.8	24	4	19	2	5
						Total		107	9	46	14	

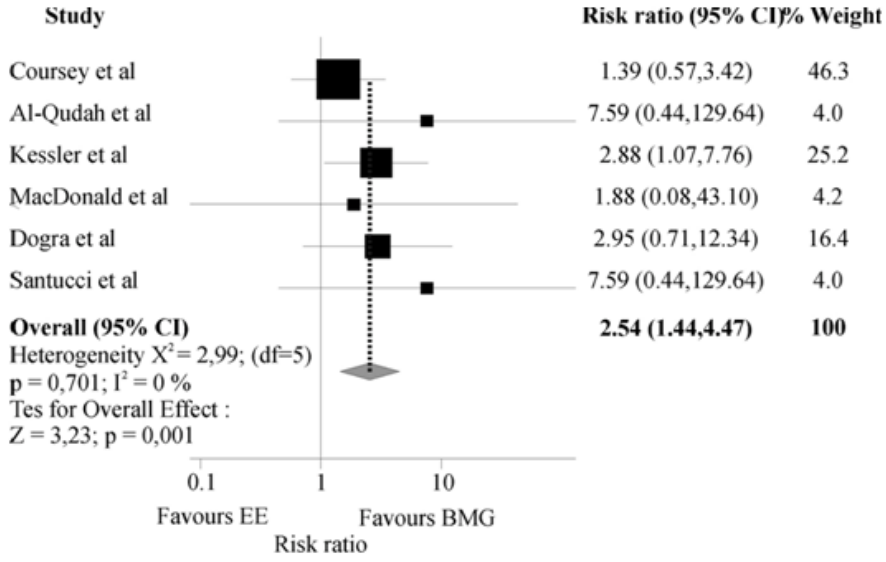

Figure 2. Forest plot comparison between EE and BMG base on sexual dysfunction

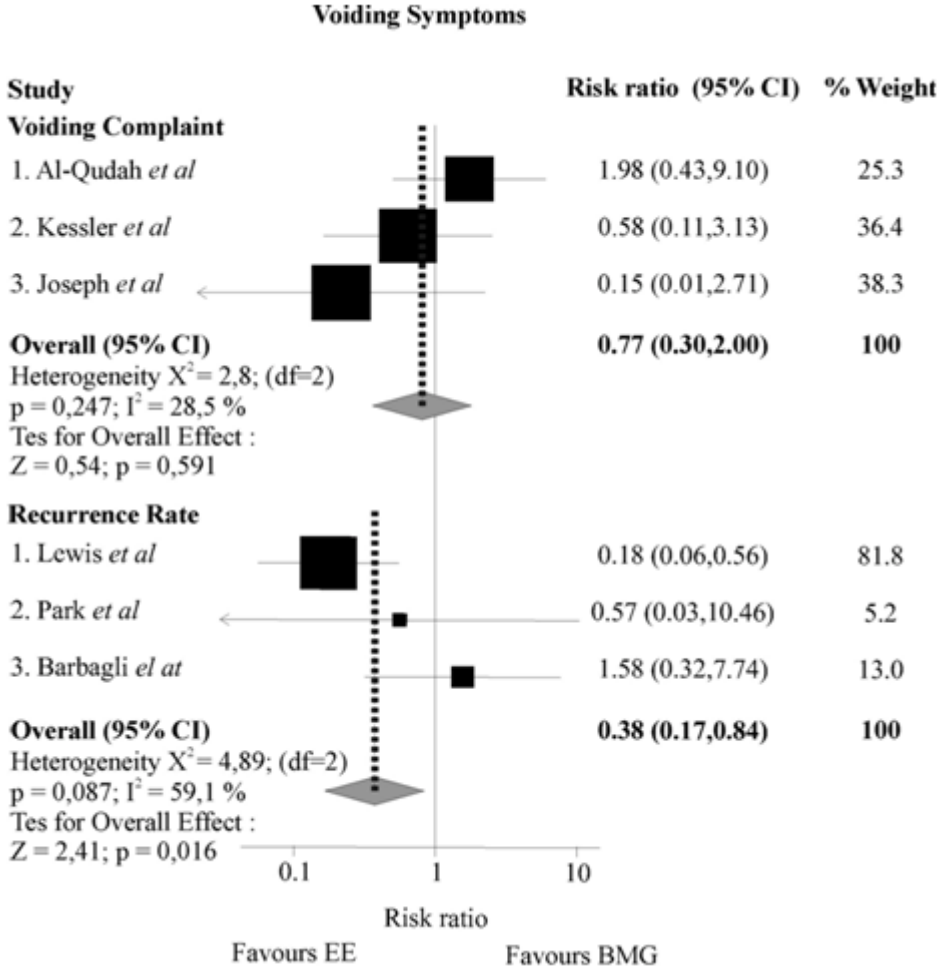

Figure 3. Forest plot comparison between EE and BMG base on voiding symptoms

idiophatic, traumatic, ischemic, inflamatory and balanitis xerotica obliterans that can predict postoperative outcome.

Based on this meta-analysis, It shows that BMG is better than EE based on sexual dysfunction in short bulbar urethral stricture (≤3 cm) management and overall risk ratio is 2.54 (95% CI 1.44-4.47). Excision of a longer urethral segment has a risk of penile shortening or chordae.[22] Chordae were reported as complication in EE and rarely in BMG.[21] We believe that neurogenic (perineal nerve), arteriogenic (bulbar artery), and psychosomatic factors play a synergistic role in sexual dysfunction after end-to-end urethroplasty.[16] The most important factor for successful urethroplasty is careful preoperative planning for a tension-free mucosa-to-mucosa anastomosis.[19]

Bulbospongiosum muscle contractions are elicited by stimulation of the dorsal nerve of the penis and following stimulation of the perineal nerve. Rhythmic contractions of the bulbospongiosum muscle expel semen and urine fron the urethra, thus avoiding semen and urine sequestration in the urethral bulb. Ejaculatory disorders may resulted from disruption of one or more of the reflex pathways providing innervation of the bulbospongiosum muscle. Due to lack of bulbospongiosum contractility, these disorders can appear as low semen expulsion pressure and decreased of semen volume.[23]

Urethral blood supply arised from internal pudendal artery, divided into the posterior scrotal artery and perineal artery, then emerges distally as the common penile artery. The proximal corpus spongiosum gets blood supply from circumflex cavernosal arteries and the bulbar arteries, branch of the common penile artery. The blood then flows into the artery dorsalis penis and central cavernosal arteries. Vascularization of the glans penis arised from the artery dorsalis penis which arborizes and penetrates the glans' spongy tissue.[24]

Sufficient blood supply and flow on the distal and retrograde are required to mobilize and transect the urethra for urethroplasty anastomosis. The longer the exicision made, the greater risk to develop chordae, penile shortening, impotence, or retrograde urethral blood flow insuficiency, although lengthening maneuvers (extensive distal and proximal mobilization, central tendon incision, and separation of corporal body) are performed.[25] Certain sexual dysfunction disorders could be manifested, such as chordate, glans insensitivity, cold glans, penile shortening, erectile dysfunction, and impotence; if the process is disturbed.[24]

Anatomical factor might play a certain role in severe erectile dysfunction after reconstruction of anterior urethra. Park et al.[19] reported from their cadaveric experiment that corpus spongiosum innervation were partly arised from cavernous nerve fiber which passed through tunica albuginea. Another parts remain about 3 mm on the outside and were located on the 1 and 11 o'clock position along the convergence of corpora cavernosa's crura. The treatment response and penile neurovascular evaluation were not not recorded on our study. Correspond with Park et al.[19] that corpus spongiosum play a minor role on erectile process, we found that buccal mucosal grafting and end-to-end primary anastomosis for bulbar stricture treatment had the most satisfying result on patient's erectile function.

Forty-seven patients were reported by Santuci et al to have undergone urethroplasty (19 buccal and 28 anterior anastomotic) with mean follow up of 36 month (range 19-60 months). In these group of patients, 0% and 18% of anastomotic urethroplasty patients had experienced early and late major complications respectively (Chordee in one patient and erectile dysfunction in 4 patients). Overall, early and late major complications have been reported to be 4% and 0% respectively.[11] Coursey et al.[13] reported there was difference in erectile angle and no difference in erectile leght. It was similar with Kessler et al[14] that found difference in penile curvature between BMG and EE.

Based on voiding symptoms in patient complaint category, there is no statistically significant difference between EE and BMG in short bulbar urethral stricture (≤3 cm) management. However, in terms of voiding symptoms in stricture recurrence rate, EE is significantly superior to BMG in the management of short bulbar urethral stricture (≤3 cm),

(p=0.016, RR 0.38 (95% CI 0.17-0.84). The explanation for this is because during EE procedur, all fibrotic tissue are excised whereas the success rate of BMG is solely dependent on the graft's scarring process (fibrotic) as well asquality and blood supply to the graft.[7,17] Smoking and chewing tobacco are factors that reduce the quality of the graft.[8]

Although voiding complaint was not statistically significant in this study, there was no recurrence rate. Excision with primary anastomosis had the highest outpatient rate (28 of 31 cases or 90%), followed by penile skin flaps (16 of 25 or 64%) and buccal mucosal grafts (10 of 22 or 45%).[18] Excision of the strictured tract and end-to-end anastomosis undoubtedly provides the best results. This technique is limited to strictures of the bulbous urethra no longer than 2 cm due to urethral mobilization, that can induce fibrosis in the urethral edges. However, a 93% success rate has also been reported in patients who had undergone previous endoscopic manipulations or with strictures longer than 1.5 cm.[19]

Barbagli et al.[26] have found that the interpretation of urethroplasty's success rate according to stricture length was controversial.[22] Barbagli and Kulkarni explained, in the Annual Meeting of the American Urology Association in Washington, United Stated, May 14th – 19th, 2011, that they performed EE on trauma induced strictures and BMG on non-trauma induced stricture during bulbar urethral stricture management.

In comparison to other grafts (e.g. penile skin, scrotal skin, extragenital skin, bladder mucosa, and colonic mucosa) buccal mucosa is superior because it is easier to harvest, more readily available, resistant to infection with favorable tissue characteristics (thick epithelium, high content of elastic fibers and thin lamina propria).[8,27]

The surgical approach is determined by the etiology, localization, extension and previous treatment of stricture as well as the availability of local skin. Urethral surgeons nowadays must be adept and experienced in performing all urethroplasty techniques to guarantee optimal treatment with the best cosmetic and functional results. In order to assure a high standard of treatment and continuity in the transmission of knowledge and skills to future urethral surgeons, all urological centers for reconstructive surgery are needed.[14]

CONCLUSION

Buccal mucosal graft urethroplasty was found to be equally effective as the end-to-end anastomosis technique with minimal complications. In terms of sexual dysfunction rate, BMG has more superior success rate than EE whereas EE has better success rate than BMG based on stricture recurrence rate in short bulbar urethral stricture (≤ 3 cm) management. Buccal mucosal urethroplasty may be considered as the primary treatment instead of end-to-end anastomosis in short strictures while awaiting for future investigation.

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